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10/601,132	06/20/2003	Anthony P. Shuber	EXT-055	4962

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EXAMINER	
AEDER, SEAN E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,132	SHUBER, ANTHONY P.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,11,14,18-21,24,27-30,32,33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) *32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 11, 14, 18-21, 24, 27-30, 33, and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 2/22/08 in response to the Office Action of 8/23/07 are acknowledged and have been entered.

Claims 35-37 have been added by Applicant.

Claims 1, 4-8, 11, 14, 18-21, 24, 27-30, 32, 33, and 35-37 are pending.

Claim 32 has been withdrawn.

Claims 1, 4, 5, 8, 14, 18, 19, 24, 27, and 28 have been amended by Applicant.

Claims 1, 4-8, 11, 14, 18-21, 24, 27-30, 33, and 35-37 are currently under examination.

Rejections Withdrawn

The rejections under 35 U.S.C. 112, second paragraph, are withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 27-30, and 33 remain rejected and amended or newly added claims 14, 18-21, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, for the reasons stated in the Office Action of 8/23/07 and for the reasons set-forth below.

The specification, while being enabling for a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, determining whether there is a statically significantly larger amount of nucleic acids greater than 200bp in length in said patient sample as compared to the amount of nucleic acids greater than 200bp in length in stool of a healthy subject wherein the presence of said significantly larger amount indicates the patient has colorectal cancer, **the specification does not reasonably provide enablement for** a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any "positive" result from said any additional assay to wherein just any "positive" result indicates said patient has cancer or has abnormal proliferating colorectal cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any "positive" result from said any additional assay to wherein just any "positive" result indicates said patient has cancer or has abnormal proliferating colorectal cancer cells.

The specification teaches a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, determining whether there is a

statically significantly larger amount of nucleic acids greater than 200bp in length in said patient sample as compared to the amount of nucleic acids greater than 200bp in length in stool of a healthy subject wherein the presence of said significantly larger amount indicates the patient has colorectal cancer (see pages 12-16, in particular).

The state of the prior art dictates that if a particular assay is to be used to determine the presence of a particular cancer, a result from said assay must be identified in some way with said particular cancer. For instance, assays using a marker, such an amount of nucleic acids greater than 200bp in length, as a surrogate for a diseased state, must identify the presence of said marker with said diseased state. There must be some pattern that would allow the marker to predictably used in a diagnostic manner with success. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. Therefore, absent evidence of results from a particular assay correlating to a particular diseased state, one of skill in

the art would not be able to predictably use a "positive" result from said assay to detect said particular diseased state without undue experimentation.

The level of unpredictability that just any "positive" result from just any assay would detect just any cancer is quite high. Since neither the specification nor the prior art provide evidence of a universal association between every positive result of every assay and colorectal cancer, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any "positive" result from said any additional assay to wherein just any "positive" result indicates said patient has cancer or has abnormal proliferating colorectal cancer cells, and Applicant has not enabled said method because it has not been shown that just any "positive" result from just any addition assay would predictably indicate that a patient has colorectal cancer or has abnormal proliferating colorectal cancer cells.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

In the Reply of 2/22/08, Applicant amended claim 24 to recite "colorectal" cancer; however, Applicant did not address how a positive result from just any additional assay would predictably indicate that a patient has cancer or has abnormal proliferating colorectal cancer cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7, 11, 14, 20, 24, 29, and 33 remain rejected and claim 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loktionov et al (Clinical Cancer Research, February 1998, 4(2): 337-342) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5) for the reasons stated in the Office Action of 8/23/07 and for the reasons set-forth below.

The claims comprise methods of detecting colorectal cancer comprising detecting genomic DNA in stool samples. It is noted that claimed methods of measuring an amount of fragments of less than 200bp broadly encompass methods of measuring

an amount consisting of fragments of less than 200bp and methods of measuring an amount comprising fragments of less than 200bp.

Loktionov et al teaches a method for diagnosing and screening a patient for the presence of colorectal cancer comprising measuring quantitative amounts of patient genomic DNA in a stool sample comprising shed cells or shed debris wherein the quantitative amounts are measured by measuring amounts of fragments of less than 200 bp. Loktionov et al teaches: (1) using PCR to detect an amount of 113 bp fragments of patient genomic DNA in a stool sample comprising shed cells or shed debris to confirm DNA quality in order to identify a patient as a candidate for additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen, before additional steps of diagnostic tests/examinations on the patient's stool sample for detecting the presence of colorectal cancer are performed (see Figure 1 and page 338 , in particular); and (2) using 260/280 nm absorbance to detect the presence of colorectal cancer by detecting a quantitative amount of genomic DNA (which would comprise fragments less than 200bp) in a stool sample comprising shed cells or shed debris by determining a 260:280 ratio (see Table 2 and Figure 2) in order to identify a patient as a candidate for additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen, before additional tests for detecting the presence of colorectal cancer are performed (see paragraph spanning pages 340-340, in particular). Loktionov et al further teaches, and one of skill in the art would recognize, that methods of screening for colorectal

cancer are methods of screening for the presence of abnormal proliferating colorectal cancer cells (see page 340, in particular).

Loktionov et al does not specifically teach genomic DNA amounts expressed in terms of "genome equivalents" or that the PCR method is "quantitative PCR". However, these deficiencies are made up in the teachings of Hromadnikova et al.

Hromadnikova et al teaches a quantitative PCR method of comparing amounts of DNA between samples comprising expressing amounts of DNA in terms of "genome equivalents" (page 2 right column, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the methods taught by Loktionov et al using quantitative PCR, and express the measured amounts of patient DNA in terms of genomic equivalents because using highly quantitative assays and expressing amounts of DNA in terms of genomic equivalents effectively normalizes data between multiple assays (page 340, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing quantitative PCR and expressing the measured amounts of DNA in the method taught by Loktionov in terms of genomic equivalents because Hromadnikova et al teaches a quantitative PCR method and methods of expressing amounts of DNA as "genome equivalents" (page 2 right column, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 2/22/08, Applicant argues that Loktionov et al does not teach or suggest isolating DNA from cellular debris. Applicant further argues that the method of Loktionov et al cannot determine a quantitative amount of all genomic DNA that is present in a stool sample because it isolates cells prior to DNA extraction and quantitation. Applicant further argues that the 260/280 nm absorbance measurement taught by Loktionov et al cannot discriminate DNA fragments based on size and is unreliable if contaminating material is present in the sample. Applicant further argues that detection of the 113bp fragment of K-ras is performed by Loktionov et al to confirm DNA quality of extracted DNA and not to determine the amount of DNA in the sample. Applicant further argues that there is no suggestion in Loktionov et al that a total complement of genomic DNA as determined by measuring an amount of nucleic acid fragments having length of 200bp or less could distinguish normal subjects from cancer patients. Applicant further argues that there is no reasonable expectation of success based on the cited art that determining genome equivalents of patient genomic DNA by measuring an amount of nucleic acid fragments having length of 200bp or less could be used as a screen to positively identify a patient as having cancer. Applicant further argues that neither Hromadnikova et al nor Loktionov et al teaches or suggests determining a quantitative amount of genome equivalents by measuring an amount of fragments having length of 200bp or less.

The amendments to the claims and the arguments found in the Reply of 2/22/08 have been carefully considered, but are not deemed persuasive. In regards to the argument that Loktionov et al does not teach or suggest isolating DNA from cellular

debris, Loktionov et al teaches isolating DNA from cellular debris that would be created upon lysing cells with lysis buffer (see top of right column on page 338, in particular).

In regards to the argument that the method of Loktionov et al cannot determine a quantitative amount of all genomic DNA that is present in a stool sample because it isolates cells prior to DNA extraction and quantitation, a quantitative amount of genomic DNA present in a stool sample comprising shed cells and cellular debris (created upon lysis) is determined by combined teachings of Loktionov et al and Hromadnikova et al.

In regards to the argument that the 260/280 nm absorbance measurement taught by Loktionov et al cannot discriminate DNA fragments based on size, the instant claims are not drawn to methods of discriminating DNA fragments based on size. Further, the 260/280 nm absorbance measurement taught by Loktionov et al would measure amounts of nucleic acid fragments, including fragments greater than and fragments less than 200 bp.

In regards to the argument that the 260/280 nm absorbance measurement taught by Loktionov et is unreliable if contaminating material is present in the sample, Loktionov et al teaches a successful working example of a 260/280 nm absorbance measurement method (Figure 2, in particular).

In regards to the argument that detection of the 113bp fragment of K-ras is performed by Loktionov et al to confirm DNA quality of extracted DNA and not to determine the amount of DNA in the sample, an amount of 113bp fragment of K-ras DNA in the sample is determined by the method taught by Loktionov et al. Again, Loktionov et al teaches a method comprising using PCR to detect an amount of 113 bp

fragments of patient genomic DNA in a stool sample comprising shed cells or shed debris to confirm DNA quality in order to identify a patient as a candidate for additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen, before additional steps of diagnostic tests/examinations on the patient's stool sample for detecting the presence of colorectal cancer are performed (see Figure 1 and page 338 , in particular).

In regards to the argument that there is no suggestion in Loktionov et al that a total complement of genomic DNA as determined by measuring an amount of nucleic acid fragments having length of 200bp or less could distinguish normal subjects from cancer patients, Applicant is arguing limitations not recited in the claims. The instant claims do not recite methods wherein the amount of nucleic acid fragments having lengths of 200bp or less distinguish normal subjects from cancer patients.

In regards to the argument that there is no reasonable expectation of success based on the cited art that determining genome equivalents of patient genomic DNA by measuring an amount of nucleic acid fragments having length of 200bp or less could be used as a screen to positively identify a patient as having cancer, Applicant is arguing limitations not recited in the claims. The instant claims do not recite methods wherein the amount of nucleic acid fragments having lengths of 200bp or less positively identify a patient as having cancer.

In regards to the argument that neither Hromadnikova et al nor Loktionov et al teaches or suggests determining a quantitative amount of genome equivalents by measuring an amount of fragments having length of 200bp or less, quantitatively

expressing the amount of 113 bp fragments of patient genomic DNA or the amount of patient genomic DNA (comprising fragments having length of 200bp or less) determined by 260/280 nm absorbance in terms of "genome equivalents" is rendered obvious by the combined teachings of Hromadnikova et al and Loktionov et al.

Claims 1, 4-8, 11, 14, 18-21, 24, 27-30, and 33 remain rejected and newly added claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loktionov et al (Clinical Cancer Research, February 1998, 4(2): 337-342) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5) as applied to claims 1, 4, 7, 11, 14, 20, 24, 29, 33, and 35-37 above, and further in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227).

Anticipation of claims 1, 4, 7, 11, 14, 20, 24, 29, 33, and 35-37 by the combined teachings of Loktionov et al and Hromadnikova et al is described above.

The combined teachings of Loktionov et al and Hromadnikova et al do not specifically teach methods of detecting the presence of abnormal proliferating colorectal cancer cells / detecting colorectal cancer / diagnosing colorectal cancer by: (1) performing a DNA integrity assay; (2) detecting a ras mutation, or (3) performing a colonoscopy. However, these deficiencies are rendered obvious or made up in the teachings of Ahlquist et al.

Ahlquist et al teaches methods for screening a patient for the presence of colon cancer comprising measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying

patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount (pages 1221-1224, in particular). Ahlquist et al teaches colorectal cancer patients have higher fecal DNA yields than controls (page 1220 left column). Ahlquist et al further teaches methods of performing a DNA integrity assay (pages 1221-1222, in particular) and an assay to detect ras, p53, and BAT-26 mutations (page 12221 right column, in particular). Ahlquist et al further teaches colonoscopies as a means of detecting colon cancer (page 1219 right column, in particular). Ahlquist et al further teaches that fecal occult blood testing may detect cancers at an early stage; however, many cancers and most premalignant adenomas do not bleed and are missed (page 1219 right column, in particular). Thus, Ahlquist et al indicate that the sensitive and specific markers they teach would improve the effectiveness and efficiency of stool screening prior to colonoscopy (page 1219 right column, in particular).

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting the presence of abnormal proliferating colorectal cancer cells / detecting colorectal cancer / diagnosing colorectal cancer taught by the combined teachings of Loktionov et al and Hromadnikova et al (described above) and perform the additional steps of performing a DNA integrity assay, an assay to detect ras mutations, and a colonoscopy taught by Ahlquist et al because Loktionov et al teaches the need for performing numerous assays to detect colorectal cancer (see paragraph spanning pages 340-341, in particular) and the assays taught by Ahlquist et al aid in the detection of colorectal cancer. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success

for perform the method taught by the combined teachings of Loktionov et al and Hromadnikova et al with a DNA integrity assay, an assay to detect ras mutations, and a colonoscopy because Ahlquist et al teaches performing a DNA integrity assay (pages 1221-1222, in particular), an assay to detect ras mutations (page 12221 right column, in particular), and a colonoscopy (page 1219 right column, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 2/22/08, Applicant repeats arguments that have been addressed above.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a). A shortened statutory period for response to this Final Action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this Final Action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. '1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response

expire later than six months from the date of this Final Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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Primary Examiner, Art Unit 1642